REMARKS

A. Rejections

1. Nonstatutory Obviousness-type Double Patenting.

Claims 21-23 are rejected under the non-statutory judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-44 of U.S. Patent No. 7,118,752; claims 1-7 of U.S. Patent No. 6,610,302; and provisionally over claims 1-23 of U.S. Patent Application Serial No. 11/354,484. The Examiner states that in each case, although the claims are not identical, they are not patentably distinct because they both encompass a method of inhibiting proliferation or reducing the invasiveness of malignant cells comprising administration of Ea-2 or Ea-4 domain peptides, wherein they may or may not be fusion proteins.

To put the present application in condition for allowance the Applicant submits a Terminal Disclaimer, accompanied herewith, in compliance with 37 CFR 1.321(c) to overcome the rejection based on non-statutory, obviousness-type double patenting. The terminal disclaimer is submitted without prejudice and is not to be construed in any way as an admission of or acquiescence in Examiner's grounds for making the rejection but rather to prompt allowance and expedite issuance of the present application. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection.

2. 35 U.S.C. § 112, First Paragraph.

a. The Examiner has rejected claim 23 under 35 U.S.C. § 112, first paragraph, on the grounds that the specification, while being enabling for methods of inhibiting proliferation and reducing the invasiveness of malignant cells *in vitro*, does not reasonably provide enablement for these methods *in vivo*.

The Examiner states that the present specification provides "no working examples of

administration of the peptide to an animal." However, the Examiner misconstrues the nature of "working examples" for purposes of enablement, and in essence, this rejection amounts to a rejection on the related basis of lack of utility.

The results of studies in model systems, including *in vitro* systems, often correlate with, and are translatable to utility *in vivo*, such as in humans, yet these models offer a system in which to manipulate and test processes, and elucidate biological mechanisms. Applicants submit that a skilled practitioner would recognize the utility of such model systems and would consider results obtained to support the specific, substantial, and credible utility asserted by the Applicants, especially because human cancer cells, and animal models were used in the working examples.

In fact, the MPEP states that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." Furthermore, the MPEP states that since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> *[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.) (Emphasis added).*

The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelsonv. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).

In the present specification, the Applicants provide numerous working examples of the efficacy of the E-peptides under conditions that reasonably correlate with *in vivo* efficacy, including experiments performed using human cancer cells, and the widely used nude mice

cancer model. Those skilled in the art widely recognize these assays as being high confidence indicators of *in vivo* activity.

In addition, the Examiner states that the claims encompass a "pharmaceutical use," and to be enabled, the specification must teach how to use for at least one "pharmaceutical use" without undue experimentation.[1] At the same time, the Examiner concedes that the present specification is enabling for the use of an E-domain peptide composition with a pharmaceutically acceptable carrier. This admission and dubious distinction undermines the Examiner's rejection *in toto*.

Applicant reminds the Examiner that even in an *in vitro* setting, use of chemical agents constitutes a pharmacological use, and therefore, would constitute a pharmaceutical use, per se. The practice of administering a pharmacologically active agent in a pharmaceutically acceptable form in an *in vitro* or *in vivo* setting (i.e., a "pharmaceutical use") is well known to those of ordinary skill in the art. As such, the Examiner has underestimated the significance of the working examples, the teaching and guidance of the specification, and the level of skill in the art.

The applicant is not required to disclose information that would be well within the skill or knowledge of one of ordinary skill in the art. Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1253 (Fed. Cir. 2004). As the Court of Appeals for the Federal Circuit determined in In re Brana, "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. 51 F.3d 1560 (1995).

The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. *In re Colianni*, 561 F.2d 220, 224 (CCPA 1977). "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In reWands*, 858

[1] The Examiner's reasoning is based on two carefully selected definitions of the word, "drug," and is inapposite to the present discussion pertaining to enablement. The word, drug, is an imprecise term whose colloquial use belies its applicability to scientific discussion. For example, "drug" can also correctly be defined as any "substance other than food intended to affect the structure or function of the body...or...a substance intended for use as a component of a medicine." ©2006 Meriam-Webster Online Dictionary. Notwithstanding the inartful definitions, Applicant maintains that the present specification sufficiently teaches and enables such uses to a person of ordinary skill.

F.2d 731, 737 (Fed. Cir. 1988). Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).[2]

The Examiner refers to In re Wands in support of the present rejection. 858 F.2d 731 (Fed. Cir. 1988). However, a proper analysis of the Wands factors, and relevant case law weighs in favor of a finding of enablement in the present case. In Wands, the Federal Circuit reversed the lower court's finding of lack of enablement because of several factors including, the specification provided considerable direction and guidance, working examples were presented, all of the methods needed to practice the invention were known, and there was a high level of skill in the art at the time the application was filed. Furthermore, In Bundy, 642 F.2d 430, 434, 209 USPQ 48, 51-52 (CCPA 1981), the court ruled that appellant's disclosure was sufficient to enable one skilled in the art to use the claimed analogs of naturally occurring prostaglandins even though the specification lacked any examples of specific dosages, because the specification taught that the novel prostaglandins had certain pharmacological properties and possessed activity similar to known E-type prostaglandins.

As discussed by the court in Wands, a specification does not fail because the teachings require some experimentation, even considerable experimentation, as long as it is not undue. Therefore, the conclusion that the experimentation is undue rests, in-part, on the nature of the technology. The Examiner concedes that the art to which the invention pertains is sophisticated, and therefore, while some experimentation may be required to identify the dosages and forms that are most efficacious *in vivo* the experimentation required would be routine, not undue, in view of the present teachings, examples, and the skill of the person of ordinary skill in the art. The specification provides a detailed characterization of an E-peptide and working examples demonstrating that E-domain peptides are useful for inhibiting the proliferation and invasion of cancer cells. Furthermore, these model systems (i.e., human cancer cells and pharmaceutical compositions) are widely employed by those of skill in the art specifically because they are accurate and economical ways of predicting *in vivo* activity and efficacy.

[2]In Teletronics, the court reversed the findings of the district court for lack of proof that undue experimentation was needed. The question of time and expense of such studies, approximately $50,000 and 6-12 months failed to show undue experimentation.

Lastly, Applicant notes that all the issued parent and related U.S. patents (i.e., 7,118,752; 6,610,302; and 6,358,916) encompass pharmaceutical and *in vivo* uses. Moreover, the related U.S. Patent 7,118,752 discloses the efficacy of the trout peptides in several *in vivo* model systems.

As such, the teachings and working examples described in the specification not only establish the E-peptide's pharmacological activity but would also be understood by a person of ordinary skill in the art to establish that a reasonable and substantial *in vivo* therapeutic/pharmaceutical use exists. Moreover, the teachings and examples provided in the specification are entirely sufficient to enable a person of ordinary skill in the art to use a pharmaceutical composition comprising E-peptides *in vivo* without undue experimentation.

Applicant believes that this grounds for rejection has been traversed and respectfully requests that the Examiner withdraw this rejection.

b. In addition, the Examiner has rejected claims 21 and 22 under 35 U.S.C. § 112, first paragraph, on the grounds that the specification, while being enabling for methods of inhibiting proliferation and reducing the invasiveness of malignant cells using Ea-2 domain peptide and Ea-4 domain peptides having the amino acid sequence of SEQ ID NOs:2 and 4, respectively, or fusion proteins comprising those amino acid sequences, does not reasonably provide enablement for E domain peptide agents, trout E-domain peptide or E-domain peptide homologs.

Although the phrase, "E-domain peptide agent" was defined within claim 21 as "selected from the group consisting of a trout E-domain peptide, a trout E-domain peptide homolog, and an E-domain fusion protein," Applicant has amended claims 21-23 to eliminate any confusion.

In addition the claims have been amended to recite a trout Ea2 or Ea4 domain peptide, a trout Ea2 or Ea4 domain peptide homolog, and a trout Ea2 or Ea4 domain fusion protein.

An applicant for a patent may include one or more "prophetic" examples, that is, specific illustrations of the invention that may not have, in fact, been carried out. MPEP § 608.01(p). As the court in held in University of Rochester v. G.D. Searle & Co., Inc., the use of prophetic examples is acceptable as long as the public can discern infringing from non-infringing compounds. 358 F.3d 916, 926, 69 USPQ2d 1886 (Fed. Cir. 2004).

Applicant submits that the teachings of the present specification and the knowledge of a

person of ordinary skill in the art at the time of filing is sufficient to enable a person of skill in the art how to make or use an Ea2 or Ea4 trout E-domain peptide homolog. A person of skill in the art would appreciate that homology of at least 30% at the primary structure level is very accurate in predicting function. Furthermore, the overwhelming majority of scientific studies relating to molecular biology, protein chemistry, biochemistry, and genetics that clearly indicates that one can accurately predict the function of a protein based on primary structural homology.

The following citations are representative examples, which illustrate the current understanding of those of skill in the art, i.e., that conservation in a polypeptide's primary structure accurately predicts protein function:

> *G protein-coupled, seven-transmembrane segment receptors (GPCRs or 7TM receptors), with more than 1000 different members, comprise the largest superfamily of proteins in the body. Since the cloning of the first receptors more than a decade ago, extensive experimental work has uncovered multiple aspects of their function and challenged many traditional paradigms. Gether U., Endocr Rev. 2000 Feb;21(1):90-113;*

> *Transcription factors share common structural motifs; the most frequent are zinc finger, leucine zipper and helix-loop-helix structures. Beyersmann D., EXS. 2000;89:11-28.*

Therefore, homologs of the claimed proteins can be easily identified by a person of ordinary skill in the art reading the present specification. The specification details key structural features of E-domain peptides, which is sufficient to enable those of ordinary skill at the time of filing the present application to make or use an Ea2 or Ea4 E-domain peptide having homology to the disclosed Ea2 and Ea4 trout E-domain peptides. For example, in paragraphs [0006]-[0012] the specification identifies the key structural aspects of the E-domain peptides and amount of evolutionary conservation in structure between several species, including human, mouse, and rat. In addition, at paragraph [0032] (Clean Version of New Specification) the specification defines E-domain peptide homologs as peptides having from between 70% to about 90% identity with a trout E-domain peptide. Support for the definition is found in the specification of the parent application, USPN 6,610,302, which was incorporated by reference.

In view of the present amendments Applicant believes that this rejection is now moot. As such, Applicant respectfully requests that Examiner withdraw this grounds for rejection.

3. 35 U.S.C. § 112, Second Paragraph.

a. The Examiner rejects claims 21-23 under 35 U.S.C. § 112, second paragraph, on the grounds that the claims do not indicate what E domain peptide is or where it is from. The Examiner suggests use of the term "E domain peptide from IGF-1," instead.

It is axiomatic that the language of the claims is construed from the perspective of a person of ordinary skill in the art in light of the specification in which they are a part. Phillips v. AWH Corp., 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). One does not look to the claims but to the specification to find out how to practice the claimed invention. W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1558, 220 USPQ 303, 316-17 (Fed. Cir. 1983).

In the present case, the specification makes it unmistakably clear to a person of ordinary skill in the art as to what an E-domain peptide is, and where it is from. By way of example, in paragraph [0006] of the specification it describes that "the primary translation product of IGF-1 mRNA contains distinct regions or domains, including...a C-terminus E domain." Therefore, Applicant believes that the meets and bounds of the claim is sufficiently clear.

Applicant believes that this grounds for rejection has been successfully traversed. As such, the Applicant respectfully requests that the Examiner withdraw this grounds for rejection.

b. Next, the Examiner rejects claims 21-23 under 35 U.S.C. § 112, second paragraph, on the grounds that the claims recite the term, "agent." The Examiner states that the distinction between an "E-domain peptide agent" and an "E-domain peptide" is unclear.

The specification and claims, as filed, make the definition of "E-domain peptide agent" clear to a person of ordinary skill in the art. Notwithstanding that fact, Applicant has amended the claims to eliminate any possible confusion.

In light of the present amendment to the Specification, Applicant believes that this grounds for rejection has been sufficiently addressed. As such, the Applicant respectfully requests that the Examiner withdraw this grounds for rejection.

CONCLUSION

Applicant has made a *bona fide* attempt to address Examiner's grounds for restriction/election and honestly believes that this paper represents a complete response and an examination on the merits is respectfully requested.

If the Examiner believes that a telephone conference with Applicants' attorneys would be advantageous to the disposition of this case, the Examiner is cordially requested to telephone the undersigned.

Applicant believes that fees in association with a two-month extension of time, and Terminal Disclaimer for Small Entity are required in association with entry of the present response. However, in the event that any fee has been inadvertently overlooked and is required, Commissioner is hereby authorized to charge any required fee or credit any overpayment to Deposit Account No. 50-3569.

Respectfully submitted,

Date: 1/26/2007

By: _____

Bryan Zerhusen, Ph.D., Esq.
Reg. No. 54,566
McCarter & English, LLP
CityPlace I
185 Asylum Street
Hartford, CT 06103
Phone: (860) 275-6735
Fax: (860) 724-3397